Remarks

Claims 1-19 were present in the application as filed. By preliminary amendment filed with the initial application papers, claim 6 was canceled and claim 20 was added, thereby resulting in pending claims 1-5 and 7-20. Claims 1-5 and 7-20 remain pending in the application.

The present invention provides a method of removing bacterial endotoxin from a specific type of pharmaceutical process solution, that is, one which contains an amphiphilic pharmaceutical drug or vaccine substance. Amphiphilic substances, particularly viral surface antigens, such as influenza surface antigens, present special challenges with respect to endotoxin removal since it is believed that, due to both having amphiphilic structures, the antigens and endotoxin become strongly associated under aqueous conditions.

To address this specific situation, the method of the present invention comprises treating the solution with an ionic surfactant at a concentration effective to dissociate the endotoxin from the amphiphilic pharmaceutical drug or vaccine substance in the solution. The resulting solution is then filtered through a molecular weight cut-off filter that has a pore size effective to retain the amphiphilic pharmaceutical drug or vaccine substance but allow the dissociated bacterial endotoxin and ionic surfactant to pass through.

Claim Rejection Under 35 USC §112, second paragraph

Claims 1-5 and 7-20 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 1 is alleged to be rendered vague and indefinite by the use of the phrase "ionic surfactant effective to dissociate the endotoxin from the amphiphilic pharmaceutical drug or vaccine substance..." Claim 1 is amended herein to recite "...an effective concentration of ionic surfactant to dissociate..." Support for the amendment is found in the specification in the paragraph which begins with the last line on page 6.

The Office Action further alleges that claims 1-4 are rendered vague and indefinite by the use of the term "vaccine substance" and queries how a "vaccine substance" differs from a "vaccine."

One of skill in the art will recognize that a finished "vaccine" product represents an assembly of a variety of components or "vaccine substances." A "vaccine," therefore, comprises some "vaccine substances" that are antigenic, i.e. the "vaccine antigens" those vaccine substances responsible for eliciting the desired immune response (the object of the vaccine), as well as non-antigenic vaccine substances, for example, those which comprise the delivery vehicle for the "vaccine antigens." Optionally, a vaccine may include additional factors, for example, adjuvant to enhance the immune response or a preservative, such as thimerosal. Hence, a finished "vaccine" comprises several component "vaccine substances," both antigenic (vaccine antigens) and non-antigenic, any of which may have become contaminated with endotoxin during preparation of the ultimate vaccine product.

Thus, Applicants believe that the terms "vaccine," "vaccine substance," and "vaccine antigen" are neither vague nor indefinite in that one of skill in the art would recognize what the term was intended to encompass.

Claim 5 is amended above to correct the lack of antecedent basis. Claim 11, as amended, no longer recites the term "analogue."

Withdrawal of the rejection of claims 1-5 and 11 under 35 U.S.C. §112, second paragraph is respectfully requested.

Claim Rejection Under 35 USC §103(a)

Claims 1-5 and 7-20 were rejected as being unpatentable over Shanbrom (EP 0 083 999) in view of Shanbrom (U.S. Patent 4,315,919).

As discussed above, the present invention addresses the specific problem of separating amphiphilic pharmaceutical substances from bacterial endotoxins which are also amphiphilic. A known problem with amphiphilic substances is that they can form strong associations with endotoxins and it is believed that complexes may be formed between endotoxins and amphiphilic substances. Consequently, it is very difficult to separate the two without adversely affecting the amphiphilic drug or vaccine substance. This is particularly true in the case of certain vaccines, for example, influenza vaccine, where the amphiphilic vaccine antigens are assembled into complexes (*e.g.*, rosettes). In the specific case of influenza antigen, it is believed that endotoxin is incorporated into the haemagglutinin/neuraminidase rosettes.

Applicants' solution to this problem, as provided by the claimed invention, is to treat the process solution with an **ionic** surfactant, and preferably, an anionic surfactant, so as to dissociate the endotoxin from the amphiphilic drug or vaccine substance. The resulting solution is then subjected to ultrafiltration such that the larger amphiphilic drug or vaccine complex is retained by the filter, while the smaller, dissociated endotoxin fragments and surfactant pass through the filter.

It will be appreciated by those of skill that a method such as Applicants' must not lead to deactivation or significant loss of the pharmaceutical drug or vaccine substance, yet must also effectively remove bacterial endotoxin and surfactant from the pharmaceutical drug or vaccine substance.

The depyrogenation method of Shanbrom ('919) suggests the use of any amphiphilic surfactant including ionic and non-ionic surfactants in conjunction with protein precipitation methods to remove the surfactant from the substance being depyrogenated. Significantly, however, the examples contained in the Shanbrom ('919) disclosure only teach the use of a **non-ionic** surfactant, Triton-X 100 (See Examples 1-5)

Similarly, the method of Shanbrom (EP) is broadly drawn to reducing or suppressing undesirable activities like pyrogenicity, hepatitis infectivity and clotting activation of biological and pharmaceutical products with a non-ionic surfactant followed by filtration. For example, Shanbrom (EP) teaches treatment of a variety of substances including depryogenation of an experimental **non-proteinaceous** polysaccharide (therefore, **hydrophilic**) vaccine with an aqueous solution of Triton 100-X (a **non-ionic** surfactant, followed by **precipitation** with polyethylene glycol 6000. A five-fold reduction in pyrogens was observed. No evaluation was made with respect to whether the vaccine's efficacy, however, was retained.

Shanbrom (EP) also teaches depyrogenation of an aqueous albumin solution using a **non-ionic** surfactant, Triton-X 100, followed by filtration. Significantly, neither Shanbrom reference provides any evidence to suggest that ionic surfactants are preferable to non-ionic. Furthermore, neither reference addresses the issue of whether filtration following depyrogenation with an **ionic** surfactant as claimed by Applicants would satisfactorily remove **ionic** surfactant from the amphiphilic pharmaceutical drug or vaccine substance. Thus, Applicants' respectfully submit that neither Shanbrom reference alone or in combination contain the necessary motivation such that one of skill in the art would use an **ionic** surfactant to remove pyrogen from an **amphiphilic** pharmaceutical drug or vaccine followed by filtration to remove the ionic surfactant from the pharmaceutical drug or

vaccine with any assurance that the ionic surfactant has been satisfactorily removed from the pharmaceutical drug vaccine substance

As has been shown herein, the deficiencies of Shanbrom (EP) are not cured by the addition of Shanbrom ('919) teachings, and even with the combination, the present invention is not achieved. Shanbrom (EP) does not disclose use of an ionic surfactant and Shanbrom ('919) fails to disclose the use of ultrafiltration as a means of separating the amphiphilic drug or vaccine substance from ionic surfactant.

For all the foregoing reasons, Applicants submit that the claimed invention is clearly distinguished from the prior art and respectfully request that the rejection under §103 be withdrawn.

There being no further issues, the application (including claims 1-5 and 7-20) is believed in condition for allowance and such action is courteously requested. Although no fee is believed due at this time, the Commissioner is authorized to charge any deficiency in fee that may be considered to be due in connection with the filing of this paper to Deposit Account 08-1935.

Respectfully submitted,

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